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INTRODUCTION

Currently, L-(^{75}Se)-Selenomethionine is used as an agent for the detection of pancreatic carcinoma, with Tc- $^{99\text{m}}$ sulfur colloid injected in addition in order to permit the subtraction of the interfering liver background from selenomethionine. But there are two serious problems about this technique, one is rather large radiation doses to the patient due to biologically and physically long half-life, 70 days and 120 days respectively. And significant number of false-positive and false-negative make routine diagnosis difficult.

Recent advances in pancreatic imaging by transmission computerized tomography have been promising, but development of new radiopharmaceuticals for the diagnosis of pancreas has been slow. Several labelled amino acid derivatives that would accumulate in the pancreas have been studied in animal experiments and in patients with pancreas disease.¹⁻⁴⁾ But these are yet far from to describe the standard effective technique.

The purpose of this study is to describe the accumulation of ^{13}N -glutamic acid to the pancreas, and its use for the imaging study of pancreas using positron emission computerized tomography.

MATERIALS AND METHODS

1) Synthesis of ^{13}N -glutamic acid

The cyclotron production of ^{13}N -ammonia and its subsequent use in the enzymatic conversion to glutamic acid by immobilizing glutamate dehydrogenase on a Sepharose support was described in detail elsewhere by K. Ishiwata et al..

2) Tissue distribution studies

Tissue distribution studies with ^{13}N -glutamic acid were carried out with male Donryu rats (weighed from 120g to 140g) and male Golden hamsters (weighed from 110g to 130g). Each experimental group consisted of six rats and four or five hamsters. Animals were fasted for 24hr and a hundred and fifty micro Ci of ^{13}N -glutamic acid was injected through the tail vein of rat and jugular vein of hamster. The animals were killed by cervical dislocation at 5, 10, 20 and 30

min. after injection. Organs and tissue samples were excised, blotted to remove adhering blood, counted in a NaI(Tl) well scintillation counter and weighed. Per cent administrated dose per tissue gram (PAD) was calculated.

An evaluation was made of the effects of various feeding protocols on the tissue activity obtained with ^{13}N -glutamic acid in the Donryu rats. The feeding protocols used were: (a) animal given standard laboratory chow ad. libitum. (24% protein, 5.1% fat, 54.5% carbohydrate). (b) animal fasted for 24hr. (c) animal fasted for 24hr followed by ingestion of high protein food (60.0% protein, 6.5% fat, 9.2% carbohydrate) for an hour before experiment. (d) animal fasted for 24hr followed by ingestion of high fat food (21.0% protein, 20.2% fat, 35.9% carbohydrate) for an hour before experiment. Water was given to each animal ad. libitum. Each laboratory chow was purchased from Oriental Yeast Co. Ltd. Tokyo.

3) Imaging studies

Miniature-pig-Gettingen 6 month old male 23kg (obtained from Clea Japan Inc.) was used for imaging studies. Pig was fasted for 24hr and anesthetized with intravenous sodium pentobarbital before experiment. Pancreas images were obtained 15 to 25 min after injection using positron emission computed tomography (ECAT-II, Ortec USA). The resolution of the system in these study was 15mm (full width half maximum) using medium resolution shadow shield and the medium resolution filter function. Scan time was 4 min per image accumulating a total of 200 to 400 K counts. Emission scans were corrected for decay and attenuation. Transmission scan with a 1.2 mCi Ge/Ga ring source performed before emission scan permit the computation of the attenuation correction.

4) X-ray CT scan

X-ray computed tomography scanning was carried out (CT scan) to obtain the anatomical reference for ECAT image. Delta 50-FS-II (Ohio Nuclear) CT scanner was used. Scanning width was 13mm. Scan time was 18 seconds. Scan was carried out under the same protocol as ECAT scan.

RESULTS

1) Tissue distribution studies

Tissue distribution of Nitrogen-13-glutamic acid showed four patterns of time activity curve (fig. 1). Blood and brain were the lowest accumulation group. Myocardium and spleen were second low but gradually increasing accumulation. Liver and kidney were high accumulation and gradual excretion pattern. Early high accumulation was observed in the kidney. High uptakes of ^{13}N -glutamic acid by pancreas and salivary gland were observed. Their uptakes increased gradually from 5 min to 30 min after injection. Pancreas to liver ratio also increased from 5 min; 1.25 to 30 min; 2.50. But in view of the half-life of Nitrogen-13, 20 min after injection will perhaps be the best time for imaging study with ECAT.

The tissue distribution of ^{13}N -glutamic acid at 20 min after injection was compared from hamster and rat to test for any possible species differences and thus to indicate the potential of ^{13}N -glutamic acid as a pancreas imaging agent in man (fig. 2). Both animals showed good pancreas uptake, pancreas to liver ratio was 1.82 for hamster and 1.92 for rat.

2) Effects of various feeding protocols

Table 1 showed the effects of various feeding protocols on the distribution of ^{13}N -glutamic acid in the rats tissues. Group C, fasted for 24hr followed by ingestion of high protein food showed both highest pancreas uptake and pancreas to liver ratio; 2.15, and also highest uptake of submandibular gland. Group A, free feeding, showed lowest uptake of pancreas, liver and submandibular gland. Highest brain uptake was observed in fasting group B.

3) Results of imaging studies and CT scan

Figure 3-a showed the ECAT image of miniature-pig with ^{13}G -glutamic acid. Figure 3-b showed the CT scan image at the same level and the same position. White arrow indicate the duodenal portion of pancreas which was clearly demonstrated as highest activity. Kidneys and left lobe of liver were also showed in the same level image.

DISCUSSION

^{13}N -glutamic acid has been studied for the imaging of human heart,⁵⁾ and osteogenic sarcoma.⁶⁾ But pancreas imaging with ^{13}N -glutamic acid and its basic study have not yet reported. In this report we described high accumulation of ^{13}N -glutamic acid in the pancreas. Time activity curve of tissue distribution indicate that glutamic acid was selectively taken into secretory gland, pancreas and salivary gland. Various feeding protocols strongly affected its uptake. These seemed to be closely related to the amino acids demand for protein synthesis after the fasting and feeding.

Per cent administered dose value of pancreas with ^{13}N -glutamic acid was almost equal to that with selenomethionine. But pancreas accumulation and pancreas to liver ratio characteristically increased according to the time after injection. Nitrogen-13 has very short physical half-life, ten minutes. It makes high dose administration possible without increased radiation dose. Combination of high dose administration and appropriate feeding protocol and suitable time after injection will make the pancreas image with ^{13}N -glutamic acid clear in future human study.

Further assessment of diagnostic value of ^{13}N -glutamic acid for the pancreas cancer, is now undertaken.

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Table 1. Effects of various feeding protocols on the distribution of ^{13}N -glutamic acids in the rat tissues. (N=6 Mean + S.D.)

% Admin.Dose/g Tissue	A free feeding	B fasted for 24hr	C fas.+high prot.	D fas.+high fat
Blood	0.158 \pm 0.051	0.170 \pm 0.015	0.247 \pm 0.115	0.122 \pm 0.088
Myocardium	0.632 \pm 0.0279	0.434 \pm 0.147	0.549 \pm 0.135	0.501 \pm 0.238
Liver	0.802 \pm 0.469	1.240 \pm 0.573	1.259 \pm 0.220	1.354 \pm 0.176
Pancreas	1.642 \pm 0.780	2.541 \pm 0.615	2.710 \pm 0.259	2.551 \pm 0.373
Kidney	1.555 \pm 0.506	1.623 \pm 0.218	2.066 \pm 0.339	1.780 \pm 0.255
Spleen	0.661 \pm 0.179	0.709 \pm 0.076	0.947 \pm 0.255	0.858 \pm 0.196
Brain	0.103 \pm 0.038	0.451 \pm 0.794	0.142 \pm 0.015	0.108 \pm 0.048
Submandibular gland	1.876 \pm 1.262	1.685 \pm 0.821	2.892 \pm 0.347	2.694 \pm 0.435
Pancreas/Liver ratio	2.05	2.05	2.15	1.89

Each data obtained 20 min after injection

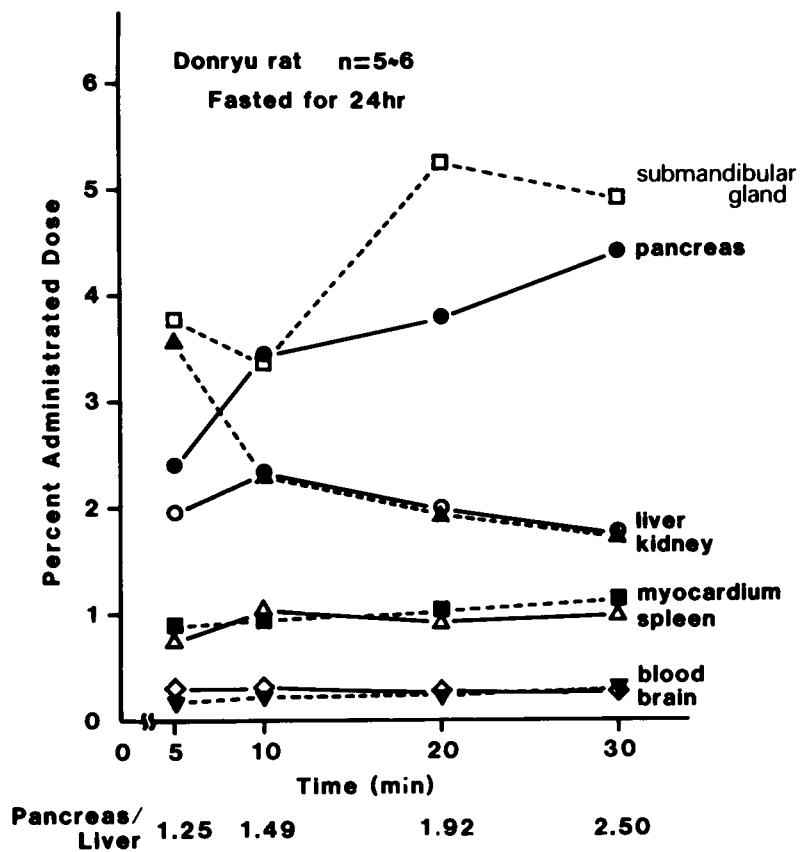


Fig. 1. Tissue distribution of ^{13}N -glutamic acid in rats.

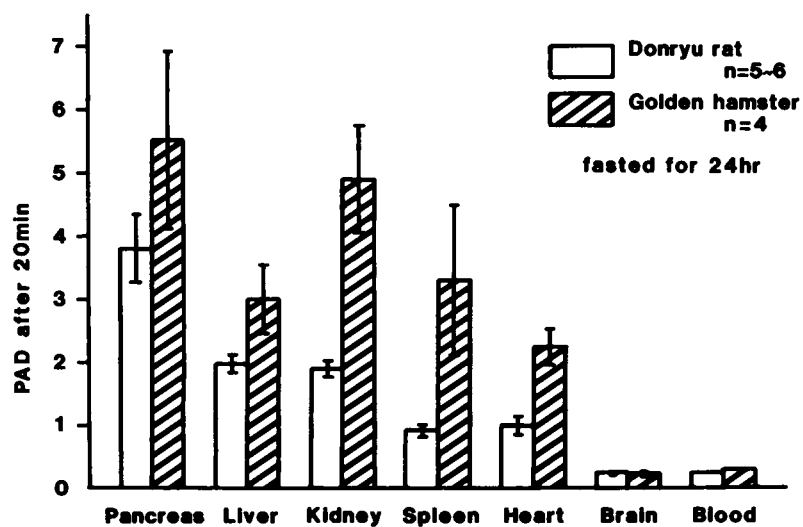


Fig. 2. Tissue distribution of ^{13}N -glutamic acid in golden hamsters and rats compared 20 min. after injection.



Fig. 3-a. Pancreas image of miniature-pig-Gettingen with ^{13}N -glutamic acid using positron emission computed tomography.

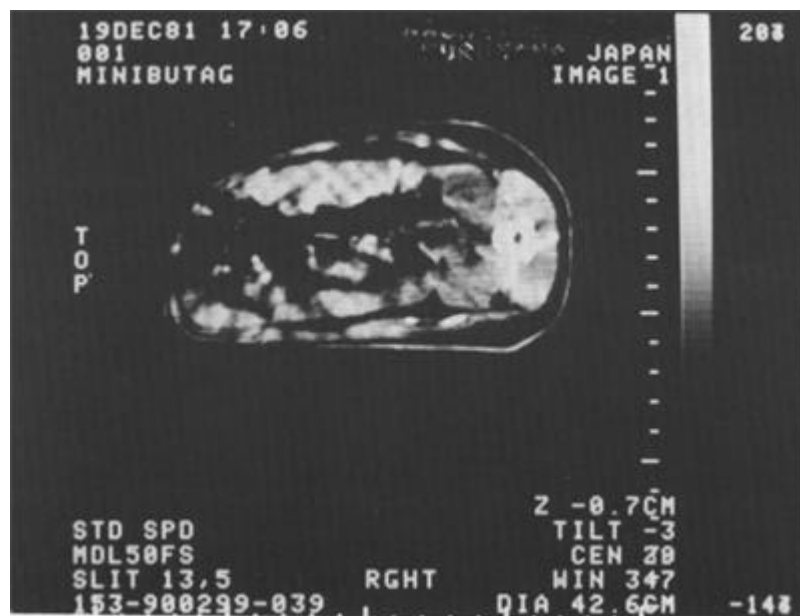


Fig. 3-b. X-ray computed tomography image of the same level and the same position of the miniature-pig-Gettingen.